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EXAMINER

HAQ, SHAFIQUK

ART UNIT

PAPER NUMBER

1641

DATE MAILED: 07/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

1. Applicants' arguments and amendment filed 5/12/06 have been acknowledged and entered.
2. Claims 8 and 13 have been cancelled and therefore, claims 1-7, 9-12 and 14-16 are pending and under active prosecution.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-7 and 9-12 and 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
5. Claim 1 recites the term "non-denaturing temperature conditions for cytokine". It is unclear what temperature (s) is/are considered as "non-denaturing temperature for cytokines" because "non-denaturing temperature for cytokines" is not defined in the specification.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over each of 1) Yuan et al (Anal. Chem. 1998, Vol. 70, No.3, pp. 596-601) or Matsumoto et al (US

5,859,297) and in view of 2) Pennanen et al (Int. J. Immunopharmacol. 1995, Vol. 17, No. 6, pp. 475-480).and further in view of Wagner et al. (US4,680,275).

The claims of the present application recite a time-resolved fluorescent immunoassay method for detection of cytokine in biological sample using a streptavidin (or avidin)-lanthanide metal ions conjugate.

Yuan et al disclose a time resolved immunoassay method for detection of alpha-fetoprotein in biological sample (serum) (see title and abstract) comprising the following: (a) anti AFP antibody (first antibody) including a portion bound to a solid-phase and a region bindable to AFP; (b) the AFP; (c) a second antibody including a region bindable to the AFP and a portion to which biotin is bound; and (d) a conjugate including streptavidin (SA) and a fluorescent structure portion (BHHCT) capable to being complexed with a lanthanide metal ion (Eu^{+3}) (see page 597, fig 1 and page 598, fig.2). The fluorescent structure portion of fig.1 (BHHT and BHHCT) anticipate formula (I) and (III) of the present application. Fluorescence is measured after composite is formed on the solid phase and both solid phase measurement and after dissolution measurement are disclosed (page 598, fig.2).

Matsumoto et al. also disclosed time resolved immunoassay method for detection (both solid phase and liquid phase measurement) of alpha-fetoprotein in a sample (see abstract and column 24, lines 15-20). The fluorescent structural portion of formulas (I), (II) and (III) of claims 1, 3 and 4 of the present inventions are disclosed in this reference (see abstract; column 2, formula (1), (2) and (3); column 19, compound (j') and (j)) that are labeled with avidin or streptavidin (column 15,

lines 55-62; column 20, lines 63-67) and complexed with lanthanide metal ions (column 5, lines 35-37 and column 25, lines 15-20). The time-resolved fluoroimmunoassay for detection of AFP includes first antibody (anti-human AFP)(column 23, line 29), human AFP (column 23, line 45), a biotinylated second antibody (biotinylated goat anti-rabbit antibody) (column 23, lines 57-58) and a streptavidin-(fluorescent structural portion)-Eu⁺³ complex (SA-BHHCT-Eu⁺³) (column 23, lines 65-66).

Both Yaun et al and Matsumoto et al. disclose that use of β -diketone ligand (BHHCT) improves detection sensitivity. Yaun et al. discloses that use of β -diketone ligand (BHHCT) gave remarkable superiority over conventional organic fluorescent labels and other lanthanide labels in time resolved fluorometric determination of AFP as the detection limits are greatly improved (page 597) and Matsumoto et al. also disclose that the use of SA-BHHCT-Eu³⁺ in a time-resolved immunoassay, remarkably improved the detection limit of AFP (from 1ng/ml to 10⁻⁶ng/ml; column 24, lines 15-25). Therefore, incorporation of β -diketone fluorescent structure portion (BHHCT) is desirable for detection of low level analytes by time-resolved immunoassay.

Although Yuan et al and Matsumoto et al. disclose detection of alpha-fetoprotein in biological sample employing streptavidin-(fluorescent structural portion)-lanthanide complex (e.g. SA-BHHCT-Eu⁺³) in time-resolved fluoroimmunoassay, but they fail to disclose detection of cytokine in biological fluids as claimed in the present applicaiton.

Pennanen et al disclose detection of cytokine in a sample by time-resolved fluoroimmunoassay comprising primary antibody (first antibody) bound to solid phase (e.g. microtiter strips), biotinylated second antibody and europium labeled streptavidin (see title and page 476, right column, lines 13-48). Pennanen et al. refer to cytokines and other cytokines (page 479, line 5 of 1st paragraph, right column) and do not exclude chemokines (i.e chemotactic cytokines).

Since, detection of cytokine by time-resolved fluoroimmunoassay using lanthanide-streptavidin complex is common and known in the art (Pennanen et al) and use of β -diketone ligand (BHHCT) is desirable in time-resolved fluoroimmunoassay as it greatly improves detection sensitivity (Yuan et al or Matsumoto et al), it would have been obvious at the time of the invention to a person of ordinary skill in the art to include cytokine as an equivalent analyte for detection in the method of Yuan et al or Matsumoto et al, with the expectation of detecting/measuring of cytokine with a high sensitivity in a sample with a reasonable expectation of success. Since it is known that cytokines are present in biological samples in low concentration, one would be motivated to use the techniques of the primary references to enhance the fluorescence detection of the low level analyte.

The above paragraphs, disclose a time-resolved fluorescent immunoassay method for detection of cytokine in biological sample using a streptavidin (or avidin)-lanthanide metal ions conjugate comprising β -diketone ligand (BHHCT) but, fail to disclose the components in a kit format.

Wagner et al. disclose time-resolved Fluorescence immunoassay method utilizing lanthanide ion such as europium or terbium chelated with organic ligand such as beta-diketone for sensitive detection of analyte in a sample. The invention also provides a reagent kit or package of materials for accomplishing an assay for an analyte in accordance with the method of the invention.

Since, packaging of immunoassay components as a kit format is common and well known in the art (Wagner et al), it would have been obvious at the time of the invention to a person of ordinary skill in the art to provide Yuan et al or Matsumoto et al with components of the immunoassay as a kit format for ease and convenience in assay performance.

Response to Argument

8. Applicant's arguments and amendments filed 5/12/06 have been fully considered and are persuasive to overcome the rejections under 35 USC 103 for claims 1-7, 9-12 and 14-15 but are not persuasive to overcome the rejection of claim 16 (kit composition) under 35 USC 103. Applicants' amendment also raised new issues under 35 USC 112, second paragraph that is discussed in paragraph 5 of this office action.

With respect to kit composition of claim 16, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fines*, 837 F.2d 1071, 5USPQ2d 1596 (Fed. Cir.

1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). In this case, both Yaun and Matsumoto disclose solid phase time resolved immunoassay method using β -diketone ligand (BHHCT) and Wagner et al. disclose that immunoassay components for solid phase immunoassay can be provided as a reagent kit or package of materials for accomplishing an assay for an analyte (see column 7, lines 29-45) and Wrangler et al. also disclose use of β -diketone ligand (see column 5, lines 1-14). Also, the packaging of components in kit form is a well-known obvious expedient for ease and convenience in assay performance and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

With respect to incorporation of term “non-denaturing temperature conditions for cytokine” in claim 1, “non-denaturing temperature” is not defined in the specification and it is not clear what temperature Applicant is intended to claim. In remarks of 5/12/06, Applicants states “heating plasma samples under non-denaturing temperature conditions leads to increased sensitivity of detection (as evidenced in figure 3b)”. Applicants’ attention is drawn to page 63, lines 12-16 of the specification, which recites “heating at 37°C or 55°C for 30 minutes yielded substantially the same calibration curve as those of the non-heated samples, and did not affect the detected amount of SDF-1”. This statement is contrary to Applicants’ remarks of 5/12/06 and Applicant is advised to clarify this statement. However,

Art Unit: 1641

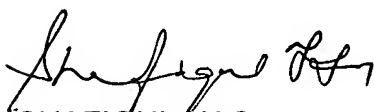
specification has guidance and examples of heat treatment of sample at 55°C for 30 minutes that results in the enhancement in fluorescence intensity (see fig. 3b and pages 13, 63 and 64) but there is no guidance and example for other conditions (i.e. heating at other temperature) that resulted in improved sensitivity.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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